ABSTRACT

Fanconi anemia (FA) is a rare genetic disorder characterized by progressive pancytopenia, congenital abnormalities, and a predisposition to malignancy. Therapy is currently limited to allogeneic marrow transplantation; patients lacking a suitable donor usually die from aplasia or acute leukemia. Recently, mutation in a novel gene named FACC (Fanconi anemia C-complementing) has been identified as causing one type of FA. FACC mutations, which introduce splicing errors or stop codons, have been identified in ~15% of FA patients. We have recently been successful in functional complementation of four FA cell lines using retroviral vectors to transfer a copy of the normal FACC gene. We also analyzed the ability of our viral vectors to functionally correct hematopoietic progenitor cells from a patient bearing a splice donor mutation. As for the lymphoid cell lines, these CD34-enriched cells were extremely sensitive to MMC. After infection of these progenitor cells with viral vectors bearing normal FACC, the progenitors gave rise to increased numbers of colonies both in the absence and presence of up to 5 nM MMC, whereas control cells were completely destroyed by 1 nM MMC. In summary, we have demonstrated that: (1) retroviral vectors can be engineered to transfer a normal FACC gene to FA(C) lymphoid cell lines and primary hematopoietic cells; (2) introduction of a normal FACC gene into CD34+ progenitors markedly enhances their growth in the absence and presence of MMC.

This study is designed to determine whether hematopoietic progenitors transduced with the normal FACC gene can be reinfused safely into FA(C) patients. CD34+ cells obtained from G-CSF mobilized peripheral blood will be transduced *ex vivo* over a 72-hour period in the presence of IL-3, IL-6, and Stem Cell Factor with the FACC retroviral vector. These transduced cells will be reinfused into FA(C) patients. Patients will be monitored for toxicities as well as evidence of successful gene transfer and expression. The procedure will be repeated up to a total of 4 times with each treatment 2-4 months apart. Theoretically, these rescued stem cells should have a selective growth advantage within the hypoplastic FA marrow environment *in vivo*.